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Studying Sleep's Profound and Extensive Effects on Brain Function

Research reveals effects of poor sleep on brain, how sleep consolidates memories

WASHINGTON, DC — Although the general benefits of a good night's sleep are well established, one-third of American adults do not get a sufficient amount of sleep. Recent research sheds new light on the extensive effects of sleep on the brain, as well as the harms caused by sleep loss. The studies were presented at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Adequate restful sleep leads to improved cognitive function and enhanced memory formation, while insufficient, restless sleep has harmful effects such as impaired memory and judgement, and can lead to increased risk for medical conditions such as stroke, obesity, and cardiovascular disease. The connection between sleep and brain function has long been an area of exploration for neuroscientists.

Today's new findings show that:

- MicroRNA expression may serve as an indicator of sleep loss in rats and humans, suggesting a possible method for predicting those at risk for diseases and cognitive deficits typically associated with sleep debt (Seema Bhatnaghar, abstract 239.25, see attached summary).
- Three species of spiders have amazingly fast circadian clocks, raising questions about how they avoid the negative effects typically associated with deviating from the normal biological timeframe (Darrell Moore, abstract 237.01, see attached summary).
- The brain preferentially reactivates negative memories during sleep, prioritizing the retention of these emotional memories (Roy Cox, abstract 431.28, see attached summary).

Other recent findings discussed show that:

- A computerized algorithm can determine whether people viewed images of faces or houses by comparing patterns of electrical activity in the brain during sleep (Monika Schönauer, abstract 193.09, see attached summary).

"Sleep is even more multifaceted and fascinating than we realize," said press conference moderator Sigrid Veasey, a professor at the Center for Sleep and Circadian Neurobiology at the University of Pennsylvania's Perelman School of Medicine. "Today's findings reveal interesting new aspects of the complex relationship between sleep and the brain, and the vital role that sleep plays in everyday human functioning."

This research was supported by national funding agencies such as the National Institutes of Health, as well as other public, private, and philanthropic organizations worldwide. Find out more about the neuroscience of sleep on *BrainFacts.org*.

Related Neuroscience 2017 Presentation
Minisymposium: Glia-Neuron Interactions Regulate Sleep
Tuesday, Nov. 14, 8:30–11 a.m., WCC Ballroom B

Abstract 239.25 Summary

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MicroRNAs May Serve as Cross-Species Indicator of Sleep Loss

Expression profiles may help identify those at risk of harmful effects caused by insufficient sleep

MicroRNA expression may serve an indicator of sleep loss in both animals and humans, demonstrating a possible pathway for determining individuals at risk for the harmful effects associated with sleep loss, according to research presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

MicroRNAs regulate gene expression in animals by preventing the production of particular proteins. Notably, they play an established role in cancer, stroke, cardiovascular disease, Alzheimer's disease, and mood disorders — all conditions that have been associated with sleep loss — and have been useful in diagnostics as biomarkers for these diseases.

In three experiments, researchers exposed humans and rats to episodes of normal sleep, shortened sleep, or total sleep deprivation (no sleep), and monitored microRNA expression via blood samples. After episodes of shortened sleep or no sleep, microRNA expression showed significant changes. In the majority of cases, expression levels returned to normal after recovery sleep. These findings, which occurred in both species, indicate that microRNAs may have potential as biomarkers of sleep debt.

Senior author Seema Bhatnagar, PhD, of the University of Pennsylvania said future work will examine "whether microRNAs can predict well-established cognitive deficits that typically occur with sleep loss." This work is part of a larger effort to determine biomarkers for sleep loss across species.

Research was supported with funds from the Department of the Navy, NASA, Clinical and Translational Research Center, Defense Advanced Research Projects Agency (DARPA), and the U.S. Army Research Office.

Scientific Presentation: Sunday, Nov. 12, 1–2 p.m, WCC Halls A–C

5612. MicroRNAs are cross-species markers of sleep loss in humans and rats

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TECHNICAL ABSTRACT: Sleep loss has been increasingly associated with diabetes, cancer, cardiovascular disease, Alzheimer's disease and mood disorders. MicroRNAs, small non-coding RNAs that are important regulators of gene expression, typically repress the expression of their target mRNAs, and play an established role in these disorders and diseases. To determine whether miRNAs are involved in sleep regulation, we examined whether they change as a function of sleep loss and recovery in humans and rats. Methods: Three highly controlled laboratory studies were performed, two employing sleep restriction (SR) and one employing total sleep deprivation (TSD). In Study 1, 15 healthy adults (35.0 ± 9.9y; 6 females), participated in a SR protocol: miRNA blood samples were taken after one 10h time-in-bed (TIB) baseline night; five 4h TIB SR nights; and one 12h TIB recovery night. In Study 2, 15 adult Sprague Dawley rats (d65-70; 8 females) participated in a SR protocol: miRNA samples were taken after one baseline night, four 4h TIB SR nights, and one recovery night. In Study 3, 12 healthy adults (24.8 ± 5.4y; 6 females), participated in a TSD protocol: miRNA samples were taken after baseline, one TSD night, and recovery. MiRNAs were analyzed via Affymetrix microarrays (Studies 1 and 2) or RNA-sequencing (Study 3). Mixed linear models with Z-score log2 fold change cutoffs of ±1.645 and greater (FDR< 0.05) were used for statistical analysis. Results: Across all three studies, a total of 45 miRNAs, 16 with increased expression and 29 with decreased expression, showed significant log2fold changes with experimental sleep loss. The majority of these miRNAs returned to baseline expression levels after recovery sleep. Notably, 17 genes targeted by miRNAs (determined from TargetScan) showed overlap across sleep loss conditions and across species. Conclusion: These results provide the first experimental evidence that miRNAs can track sleep loss and recovery dynamics across species and serve as epigenetic biomarkers of sleep debt. This work establishes a definitive link between miRNA expression profiles and known diseases resulting from sleep loss.

Abstract 237.01 Summary

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Spiders With Strikingly Fast Circadian Clocks Defy Biological Norms

Scientists hypothesize spiders somehow counteract negative effects of deviating from standard 24-hour clock

Scientists recently discovered that three species of spiders possess among the shortest naturally occurring circadian clocks on record, according to new research released at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health. In fact, the spiders' circadian clocks are so much faster than the standard 24 hours that, according to contemporary understanding of biological time-keeping, these spiders should struggle to survive.

Circadian clocks regulate the activity of most organisms on Earth, from cyanobacteria to fungi, plants, and animals, including humans. These internal biological clocks usually cycle with a period close to 24 hours, or the length of the solar day, and enable organisms to schedule, without conscious thought, the best time of day to eat, sleep, avoid predators, secrete hormones, and perform many other functions. Experimental evidence has shown that organisms with circadian clocks deviating too far from this 24-hour cycle are typically at a distinct disadvantage.

Researchers identified three closely related spider species, two trashline orb-weavers (*Allocyclosa bifurca* and *Cyclosa turbinata*) and one spiny orb-weaver (*Gasteracantha cancriformis*), with biological clocks that averaged 17.4, 18.5, and 19.0 hours, respectively. The researchers hypothesize that these spiders must have found a way to avoid the negative effects of running at such a fast speed or that there is a counter-balancing advantage associated with short-period clocks specific to these species.

Their research reveals that all three species show a major late-night activity peak, contrasting with the bulk of activity occurring in early night in other nocturnal spiders. In nature, trashline orb-weavers replace their webs 3-5 hours before dawn. Because trashline orb-weavers likely descended from orb-weavers that replace their webs at dawn, the researchers note, the shorter circadian clock may have enabled a switch from dawn to pre-dawn web-building, providing an advantage by avoiding diurnal predators during the early morning hours.

"By determining the differences between short- and normal-period circadian clocks in spiders, we may gain insights into how and why circadian clocks in general are modified to fit the particular environmental challenges of each species," said lead author Darrell Moore, PhD, of East Tennessee State University.

Research was supported with funds from the National Science Foundation.

Scientific Presentation: Sunday, Nov. 12, 1–2 p.m., WCC Halls A–C

11798. Life in the fast lane: Exceptionally short-period circadian clocks in orb-weaving spiders
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TECHNICAL ABSTRACT: It is widely believed that possessing a circadian clock is adaptive because it enables organisms to schedule physiological and behavioral changes in anticipation of daily environmental events. Most endogenous circadian oscillators "resonate" with the solar cycle by expressing periods very close to the 24-hour daily period. Experimental evidence has shown that organisms with circadian clocks deviating from resonance typically have reduced fitness. Recently, we discovered that two closely related, trashline orb-weaving spider species, *Allocyclosa bifurca* and *Cyclosa turbinata*, and one spiny orb-weaving species, *Gasteracantha cancriformis*, have exceptionally short-period endogenous rhythms of locomotor activity under constant dark (DD) conditions, averaging 17.4, 18.5, and 19.0 h, respectively. These may be the shortest, or among the shortest, naturally occurring circadian periods on record and are comparable to the laboratory-generated 20- and 18-h mutants in hamsters and the 19-h per^S mutant in *Drosophila*, yet these spiders were collected from natural populations in the field. In theory, being so far out of resonance with the 24-h day, these species should not exist. Our data show that three other species of orb-weavers and two species of cobweb spiders have circadian clocks with more typical free-running periods. Further setting the short-period orb-weavers apart from all other spider species studied thus far is their pattern of entrainment to light-dark (LD) cycles. All three short-period species show a major locomotor activity peak in late scotophase (night), contrasting with the bulk of activity occurring in early scotophase in other nocturnal spiders. Experiments shifting the relative positions of the lights-on and lights-off transitions revealed that the lights-off (dusk) transition is the primary entrainment signal. We hypothesize that entrainment is accomplished by large (5-7 h) phase delays from light exposure during the late photophase, just preceding dusk. Evidence supporting or refuting this hypothesis will be obtained by generating a phase response curve to light pulses. With respect to the possible adaptive significance of the short-period clocks, we have observed that our two trashline orb-weavers replace their webs 3-5 h before dawn (corresponding to the late-scotophase locomotor activity peak). Because our trashline orb-weavers likely descended from orb-weavers that replaced their webs at dawn, the short-period clock may have facilitated a switch from dawn to pre-dawn web-building, providing a selective advantage through a reduction in predation from diurnal predators during the early morning hours.

Abstract 431.28 Summary

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Brain Preferentially Reactivates Negative Memories During Sleep

Study increases understanding of how emotional memories are selectively stabilized during sleep

The brain selectively reactivates negative memories during sleep, prioritizing the retention of these emotional memories, which may be of greater future relevance than neutral memories and thus more worth remembering, according to new research presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

Over the past two decades neuroscientists have developed an increased understanding of how sleep boosts and stabilizes memories in the human brain. In the current study, researchers presented 57 healthy volunteers with a series of neutral and negative images. While staring straight ahead, the volunteers saw all of the negative images on one side of their field of vision (e.g., left) and all of the neutral images on the other side (e.g., right). Because our brains process visual information in the opposite hemisphere from where it is viewed, this method allowed researchers to "tag" one hemisphere with negative content and the other with neutral content, enabling them to track localized memories.

Participants were then shown the previously seen images for memory tests — with some of the images shown immediately after the learning phase and the rest shown after a period of either wakefulness or sleep. During all memory tests, volunteers viewed the images directly in front of them, rather than to either side, and researchers asked participants to state whether an image had originally appeared to the left or right. Participants who stayed awake in between memory tests forgot some of the original image locations, but forgetting was similar for neutral and negative images. Participants who slept between tests, on the other hand, had a much better rate of recall for the negative images, than the neutral ones.

Electroencephalography (EEG) recordings taken during the learning phase show the brain has encoded the distinct types of memories in its two different hemispheres, with the negative images strongly encoded in the hemisphere opposite to the side of presentation. Researchers are now analyzing data that they hypothesize will show that the waking EEG pattern corresponding to emotional memories is the same pattern that is reactivated most strongly during sleep.

"This would provide a long sought-after brain-based explanation of how sleep selectively stabilizes emotional memories," said lead author Roy Cox, PhD, of Beth Israel Deaconess Medical Center and Harvard Medical School, in Boston. "Our research substantially advances the notion that sleep plays a fundamental and complex role in the offline reorganization of waking experiences."

Research was supported with funds from the Netherlands Organization for Scientific Research and the National Institute of Mental Health.

Scientific Presentation: Monday, Nov. 13, 4–5 p.m., WCC Halls A–C

12889. Sleep selectively enhances associative aspects of emotional memories
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TECHNICAL ABSTRACT: **Introduction** – Sleep promotes the retention of episodic memories, but prioritizes memory stabilization depending on items' perceived relevance. Typically, emotional material benefits more from a period of sleep than neutral information. At a more fine-grained level, however, it is unclear which aspects of emotional memory are preferentially consolidated. Here, we test whether selective consolidation effects differ for item recognition and associative memory. **Methods** – Forty-five healthy volunteers encoded 128 neutral and 128 negative stimuli presented visually to either the left or right visual field, with separate groups encoding in the morning (n=16) and evening (n=29). Immediately after encoding, and after a 12 h interval containing either sleep or wake, individuals were shown items that were presented before as well as new items. Crucially, items were now presented centrally, not lateralized. Subjects judged each item in two distinct ways. First, to measure item recognition, subjects provided an old/new rating. Second, to measure associative memory aspects, they indicated the side where they believed the item was originally presented. We analyzed behavioral data by performing several 2 (GROUP: sleep/wake) x 2 (VALENCE: emotional/neutral) x 2 (TIME: immediate/delayed) mixed ANOVAs. In addition, we recorded high-density EEG in the sleep group throughout the encoding, retrieval, and sleep periods, to search for neural correlates of sleep-dependent memory effects. **Results** – Source memory for correctly recognized old items was selectively enhanced for emotional items over a period of sleep vs. wake. This was expressed as a significant 3-way interaction between all factors (P=0.004). Follow-up tests demonstrated that while associative

memory performance decreased across time for emotional (P=0.015) and neutral items (P=0.10) in the wake group, and for neutral items in the sleep group (P=0.001), source memory improved significantly for emotional items across sleep (P=0.035). In contrast, changes in recognition memory over time did not depend on whether subjects slept or not, either for emotional or neutral items. EEG oscillatory correlates underlying behavioral consolidation effects will be presented. **Conclusion** – These results of selective strengthening of associative links for emotional items during sleep are consistent with theoretical accounts of sleep's role, recoding labile, hippocampus-dependent, relational memories to a more stable neocortical format.

Abstract 193.09 Summary

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Computer Algorithm Assesses Patterns of Brain Activity During Sleep

Machine learning method successfully determined which set of images participants viewed before sleep

A computerized algorithm can determine whether people viewed images of faces or houses by comparing patterns of electrical activity in the brain during sleep, according to recently published research presented today at Neuroscience 2017, the annual meeting of the Society for Neuroscience and the world's largest source of emerging news about brain science and health.

The brain replays previous experiences while we sleep in a process believed to strengthen memory formation. Most memories activate networks of neurons rather than individual neurons, making the exact roles of the various parts of the brain in memory formation hard to discern.

In this study, researchers presented volunteers with images of either faces or houses. All participants then slept for 8 hours, during which time researchers conducted high-density electroencephalography (EEG). The EEG recordings revealed stable patterns of activity during both the REM and non-REM (slow wave) phases of sleep. However, these patterns varied depending on whether participants had viewed faces or houses and were traceable to different parts of the brain. Based on this information, the researchers developed an algorithm that could successfully identify which set of images new participants had seen prior to sleep, based strictly on their EEG brain activity. Further study is needed to elucidate the unique purposes of REM and non-REM sleep in memory formation.

"Pattern recognition is a highly sensitive method that is becoming more and more widely adopted in the life sciences," said lead author Monika Schönauer, of the University of Tübingen, in Germany. "It is likely that it will enable more breakthroughs especially in cognitive neurosciences, where it allows us to investigate previously hidden processes like dreams and spontaneous thought processes."

Research was supported by the Deutsche Forschungsgemeinschaft and Bernstein Center for Computational Neuroscience.

Scientific Presentation: Sunday, Nov. 12, 3–3:15 p.m., WCC 156

11248. Decoding material-specific memory reprocessing during sleep in humans
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TECHNICAL ABSTRACT: Experiments in animals found that learning-related neuronal activity is replayed during sleep. This process is thought to stabilize new memories. Activity on the level of brain areas suggests similar reactivation in humans. Whether brain activity in human sleep actually reflects the specific content of previous learning episodes, however, remains unclear. To detect such material-specific memory reprocessing, we developed a multivariate pattern classification (MVPC) algorithm that can determine what type of images participants had viewed in a learning session based solely on brain activity during sleep. In our experiment, 32 subjects learned pictures of either faces or houses before an 8-h period of nighttime sleep during which brain activity was recorded with high-density EEG. We then employed MVPC methods to test whether electrical brain activity contains information specific to the previously learned material. We find significant patterns of learning-related processing in the EEG of rapid eye movement (REM) and non-REM (NREM) sleep, which are generalizable across subjects. This reprocessing occurs in a cyclic fashion during time windows congruous to critical periods of synaptic plasticity. Its spatial distribution over the scalp and frequency composition differ between NREM and REM sleep. Moreover, only the strength of reprocessing in slow-wave-sleep predicts later memory performance, speaking for at least two distinct underlying mechanisms in these states. We thus demonstrate that memory reprocessing occurs in both NREM and REM sleep in humans, and that it pertains to different aspects of memory consolidation.